Chapter 4

Peritonectomy Procedures and HIPEC for Peritoneal Metastasis from Ovarian Cancer

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Additional information is available at the end of the chapter

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Abstract

Peritoneal carcinomatosis (PC) is the most impressive and frequent evidence of loco-regional spread of epithelial ovarian cancer (EOC). For most of its natural history, PC remains confined to the peritoneal district, thus representing a target for various combinations of surgery and systemic or loco-regional chemotherapy. PC is observed both in primary settings, i.e. in patients first treated for locally advanced EOC, and in recurrent, previously treated, EOC patients at any FIGO stage. Since 2000s, the use of hyperthermic intraperitoneal chemotherapy (HIPEC) combined with maximum cytoreduction (peritonectomy) has gradually spread in the treatment of PC from ovarian cancer, as well as for gastrointestinal carcinomatosis and primary tumours of the peritoneum. Use of combined peritonectomy + HIPEC in the treatment of ovarian carcinomatosis is the most discussed issue among those concerning peritoneal surface malignancy (PSM). The main criticism concerns the use of HIPEC, since the need for maximal cytoreduction is consolidated and does not raise any doubts. Communities of surgeon and oncologic gynaecologists who believes in the role of HIPEC have started controlled clinical trials aimed at clarifying the role of HIPEC associated to peritonectomy, but these studies are difficult to conduct and time-consuming. At present and pending the results of future prospective trials, the role and limits of application of the procedure are drawn from experiences from three basic study groups: collective reviews, multicentre studies, monocentric case studies produced by high-volume HIPEC centers. A comprehensive literature review and an in-depth

analysis of our personal experience, based on the largest monocentric case series (130 cases), have helped to provide an assessment on the role of peritonectomy + HIPEC in about 2000 patients treated for initial and recurrent PC from ovarian cancer. Comparison of the overall results drawn from these studies, indicates that peritonectomy + HIPEC is able to guarantee in these patients better overall survival (OS) and higher progression-free survival (PFS) rates than those derived from traditional treatments, with acceptable morbidity and mortality. Notwithstanding, some specific aspects, including the role of chemoresistance and neoadjuvant and adjuvant treatments, should be clarified by further experience and the results of on-going trials.

Keywords: Epithelial Ovarian Cancer, Peritoneal Carcinomatosis, Peritonectomy, HIPEC

1. Introduction

Peritoneal metastasis is the most common type of diffusion and the most frequent cause of death from EOC.

Intra-abdominal and pelvic parietal and visceral peritoneal metastases, often associated with ascites, resectable hepatic metastasis, deep bowel wall infiltration up to mucosa, identify stage III or IV ovarian cancer with diffuse PC [1,2]. Treatment of these conditions is traditionally based on cytoreductive surgery (CRS) combined with systemic carbotaxol-based chemotherapy at first line. Despite high rates of chemosensitivity, relapses are detected in up to 50% of cases in the first two years and in almost 100% in the first 5 years post-treatment. [3]

For most of its natural history, EOC is confined to the abdominal cavity, developing further peritoneal tumour implants and producing pelvic and lumbar lymph node metastases without extra-abdominal diffusion.

For this reason, new integrate therapeutic strategies have emphasized the role of local aggressive treatments, represented by maximal cytoreductive surgery (peritonectomy) combined with loco-regional HIPEC.

Peritonectomy (PRT) associated with HIPEC has been used since the second half of the 90's in the treatment of ovarian PC, as well as in other primary and metastatic peritoneal surface malignancies.

PC is observed both in primary settings, i.e. in patients first treated for locally advanced EOC, and as a recurrence in patients previously treated for ovarian cancer at any stage.

2. Initial and recurrent ovarian carcinomatosis

About 75% of ovarian cancers are diagnosed and treated in primary settings as FIGO Stage IIIc/IV, meaning that they are confined to the abdominal and pelvic cavity and characterised

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by diffuse visceral and parietal PC [4]. PC is frequently associated with lymphnode metastases and less commonly with haematogenous hepatic metastases.

Such a high percentage of PC at first presentation is mainly caused by the relevant delay in diagnosing EOC at early stages, due to the lack of symptoms and to the low sensitivity and specificity of diagnostic tools. Only 20% to 30% of EOC in developed countries are diagnosed at FIGO Stage I and II and the diagnosis is usually accidental: either via sonography, computerised tomography (CT scanning) or during laparoscopic investigations [5,6].

The pathogenesis of late PC in patients already treated for EOC at any stage is more complex.

At FIGO stages I and II it may be related to a number of factors:

1. Limited and incorrect application of standard surgical procedures;

2. Inherent limitations to the procedures established by international guidelines;

3. Chemoresistance.

Point 1 of the above is sometimes dictated by special clinical situations, which require conservative treatment. Young patients with small ovarian tumours can be treated with simple unilateral oophorectomy, in order to preserve their reproduction function. The results of this strategy are not uniform and tend to show an unjustifiable risk of surgical relapse. Rupture of the ovarian tumour during open surgery, or more often during laparoscopic surgery, is one of the most frequent cause of peritoneal recurrence [7].

Omission of appendectomy or total omentectomy is also not a rare cause of peritoneal recurrence or persistence of the disease (Fig. 1).

As to point 2, despite international guidelines advice for infra-colic limited resection of the greater omentum and for not total omentectomy, the presence of histologically-proven tumour implants in the latter tissue is associated to elevated rates of peritoneal and omental recurrence.

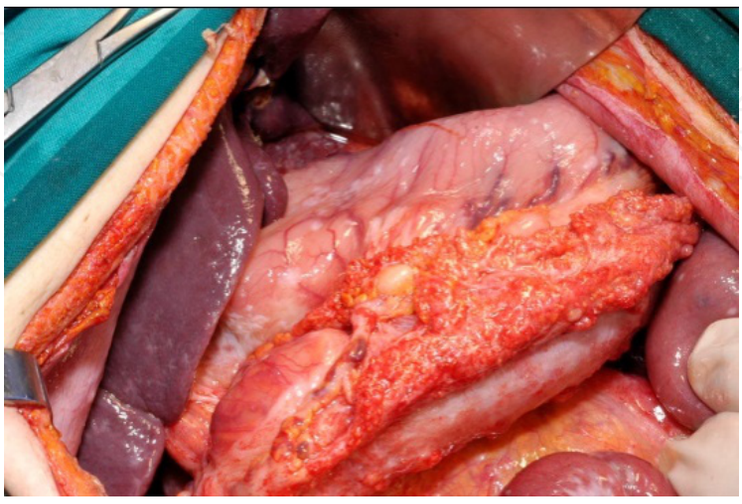

Figure 1. Residual greater omentum involved in recurrent peritoneal carcinomatosis.

On the other hand, the anatomical structure of the omentum is unitary and limited resection is, therefore, not plausible. It should be reminded that the omentum often harbours EOC deposits by virtue of its peculiar anatomy and function. It contains milky spots, which are responsible for the concentration and reabsorption of intraperitoneal fluid, including malignant ascites. It is through the milky spots that the tumour cells take root into the omentum. This phenomenon facilitates the formation of carcinomatous nodules of various sizes, in some cases involving the complete replacement of the omental tissue with tumour tissue ("omental cake").

Omission of lymphadenectomy in early stage EOC is frequent and correlates significantly with subsequent loco-regional lymph-node metastases and PC (over 50% in our series of recurrent EOC patients).

Finally, chemoresistance to first-line adjuvant treatments with carbotaxol is detectable in 20% of cases and is a further cause of relapse after treatment for stage I and II EOC [8].

Peritoneal recurrences after treatments for FIGO stages III or IV intraperitoneal EOC, can be mainly attributed to the lack of aggressiveness of the standard treatments. The current standard therapy, i.e. CRS combined with systemic chemotherapy, shows limited efficacy in high stage EOC, and is followed in most cases by abdomino-pelvic loco-regional recurrence.

Most often relapses occur as PC, associated with ascites in 60% of cases.

Further attempts to treat ovarian cancer at stage III — aimed at curbing the incidence of peritoneal recurrence — involve the use of intra-peritoneal normothermic chemotherapy (IP CHT).

Several randomized trials have demonstrated the effectiveness of this method, especially after optimal CRS; nevertheless it is still rarely used mainly due to catheter-related complications which significantly reduce its applicability. [9,10]

In conclusion, PC is the most frequent and characteristic manifestation of EOC, whether identified early at first assessment or later as persistent or recurrent disease following standard treatments. These include surgical debulking and systemic chemotherapy, are characterised by high recurrence rates and cannot guarantee long-term survival and improvement in the quality of life.

3. Epidemiology

EOC affects over 200.000 women and causes 125.000 deaths annually worldwide, with a deaths/new cases ratio of 62,5 % [11]. These data demonstrate that standard treatments are not able to deal effectively with this disease, and success rates are distant from other common types of cancer, such as colorectal cancer, for which the deaths/new cases ratio was 45.9% over the same period. The low impact of standard treatments is also corroborated by the analysis of the causes of death for EOC patients. Our National Institute of Statistics (ISTAT) data referred to 2013-2014 showed that 80% of deaths in EOC patients is exclusively due to peritoneal recur-

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rence, 10% to peritoneal recurrence associated with extra-peritoneal metastasis, and only 10% exclusively to extra-peritoneal metastases. Therefore, alternative therapeutic strategies are needed, also considering that distant metastases are a late occurrence in EOC patients, mainly due to the little effectiveness of standard treatments.

4. Macroscopy and microscopy

Traditionally the origin of carcinomas of the ovary is identified in the Ovarian Surface Epithelium (OSE). Growing evidence indicates that the majority of EOC have an extraovarian source. [12]

The new paradigm that increasingly fits with the extraovarian origin of EOC establishes common characteristics for ovarian, tubal and primitive peritoneal tumours that unite these malignancies in a common family, divided into two broad groups: type I and type II ovarian cancers.

Molecular profiling contributes to better distinguish the two types of ovarian cancer (high grade vs. low grade) as well as identifying various subtypes, i.e., serous, mucinous, endometrioid and clear cell cancer.

The application of these new classifications will be invaluable in identifying "ovarian" tumours with different prognosis and targets for specific therapeutic strategies. [10]

Major studies on ovarian PC include ovarian, tubal and primitive peritoneal carcinomas grouped together due to their histological and pathological similarities and the treatment options which are identical for all three forms.

Macroscopically the ovarian carcinomatosis is similar to other forms of PSM. It can be present as nodules varying in size from less than 1 mm to various centimetres, isolated or conglomerated in the form of solid or cystic masses or plaques of varying sizes and thicknesses.

The serous or mucinous content of carcinomatous implants and their degree of invasiveness of the peritoneum and of the underlying structures is extremely variable.

Previous treatments with chemotherapy can influence the appearance of ovarian carcinomatosis. After neoadjuvant or adjuvant chemotherapies, the peritoneum can show evident signs of carcinomatosis regression on its surface, ranging from significant reduction to complete disappearance; in each case the signs of previous disease are still evident.

In particular, the increase in thickness of the parietal and visceral peritoneal membrane, its opacification, and the presence of blurs and reddish spots indicate the location and extent of previous carcinomatosis.

Histological and immunohistochemical studies of biopsies of these tissues often show the presence of microscopic foci of disease in the context of thick, fibrotic areas.

These macroscopic and microscopic features are potential justifications for relapse after neoadjuvant or adjuvant chemotherapy in patients subjected to an apparently negative

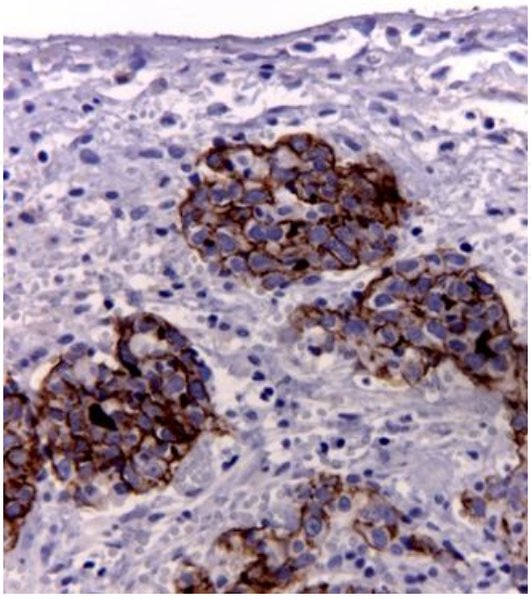

Figure 2. Microfocus of neoplastic cells inside fibrous desmoplastic tissue- CA-125 immunohistochemistry.

second-look. Indeed, fibrosis encapsulating foci of neoplastic cells may preserve them from effects of further systemic or locoregional therapies.

Furthermore, total chemical cytoreduction runs the risk of both surgical and chemotherapic undertreatment, especially if obtained after effective neoadjuvant treatments.

PC may involve any anatomic site and bowel segment or parenchyma in high percentages (parietal and visceral peritoneum 90%; omentum 60%; diaphragm 40%; liver and spleen capsule 15%). Lymphatic and haematogenous metastases in the liver may also be detected contemporaneously (respectively 50-60% and 5%). Ascites is present in about 60%.

5. Diagnosis and staging of peritoneal carcinomatosis

The ovarian carcinomatosis is paucisymptomatic until it assumes a considerable size or is associated with ascites or occlusion. Therefore diagnosis is often delayed and more than 70% of ovarian cancer patients are diagnosed at FIGO stages IIIC/IV.

Clinical examination with vaginal and rectal exploration plays a critical role in assessing the pelvic spread of the disease.

Diagnosis is based on a set of efficient morphological investigations (CT, MRI, PET). CA 125, in association or not to CA 19.9, and currently to HE-4, are the most sensitive tumour markers for specific diagnosis of ovarian cancer. Laparoscopy plays an important role in doubtful cases, allowing the direct visualization and biopsy of suspected lesions.

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The intraoperative staging of PC from ovarian cancer, as in other forms of PSM, relies mainly on PCI classification proposed by Sugarbaker [13], although other classifications have been proposed.

The correct staging of PC is important to assess resectability, prognosis and risk of complications. For this reason, much effort is made to adopt the PCI classification also prior to surgery by applying it to data from morphological imaging (CT, MR, PET) or laparoscopy investigations.

Being able to determine reliably in the preoperative phase the peritoneal spread of the disease and the involvement of sensitive anatomical areas, PCI could avoid unnecessary surgical approaches and improve the overall strategy as well as identify cases to be submitted to neoadjuvant chemotherapy (NACT).

However results are still unsatisfactory both due the complexity of PCI classification and the difficulty in its preoperative application; recently a new and simpler method to stage peritoneal carcinomatosis via laparoscopy has been proposed [14].

If the above described set of diagnostic procedures increases the percentage of successful diagnosis of PC, including the identification of the primary tumour and the eventual presence of extra-peritoneal disease, the reliability of the current standard diagnostic tools used in staging intraperitoneal spread must be considered as unsatisfactory. Many authors emphasize the role of laparoscopy in staging intraperitoneal spread of carcinomatosis, but the obvious limits of feasibility in pervasive forms of recurrence restrict the use and significance of this method [14-17]. Moreover risk of contamination of port site access by tumor cells at laparoscopy should be considered [18-20].

6. Evaluation of residual disease after cytoreductive surgery

Evaluation of tumor residues after cytoreductive surgery is of relevant importance because of residual disease volume is the major prognostic factor in the treatment of EOC.[21-30]

The degree of cytoreduction can be assessed with various classification systems, the most used of them is the Sugarbaker scoring classification [Completeness of Cytoreduction score (CC)] [31]. This system provides four values from 0 to 3, where 0 indicates complete cytoreduction of peritoneal carcinomatosis with total absence of macroscopic residual disease at the end of the surgical phase. The maximum therapeutic efficacy of the integrated procedure is carried out in cases where an ”optimal” cytoreduction (CC0 - CC1) is achieved.

7. Peritonectomy and HlPEC

The limits of success of standard treatments of PC from ovarian cancer have led to test new therapeutic possibilities, borrowing from the experiences made in other forms of peritoneal

carcinomatosis a therapeutic strategy based on the association of maximal cytoreduction (Peritonectomy) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

Peritonectomy is aimed to complete removal of macroscopic disease; HIPEC is aimed to treat microscopic or millimetric tumor residues after surgical cytoreductive phase.

7.1. Rationale

The association between PRT and HIPEC is based on a complex rationale that takes into account the mechanism of intraperitoneal spread of free cancer cells, Gompertzian tumor growth kinetics, Goldie&Coldman mathematical model about drug resistance, pharmacokinetic and pharmacodynamic events related to intraperitoneal chemotherapy associated with hyperthermia. [32]

Maximal cytoreduction reducing drastically tumor volume, induces the remaining cells to enter the fast proliferating phase of the cell cycle becoming more responsive to chemotherapic drugs. Moreover microscopic or millimetric residual tumor volumes include a minor rate of chemoresistant clones and can be totally permeated by drugs delivered by intraperitoneal chemotherapy [33-36].

The association of HIPEC is based on a series of advantages related by a part to the fact that the chemotherapy is carried out at the end of the surgical stage directly into abdominal cavity and by the other part to the fact that drugs used are brought to a constant temperature of 42-43° for the entire treatment period of infusion (usually 60 minutes).

The benefits of loco-regional chemotherapy consist of:

- direct exposure of whole anatomical region to chemotherapy being absent adhesions
- possibility of using high concentrations of chemotherapics
- possibility of allowing a prolonged exposure time
- low systemic toxicity

The combination of hyperthermia provides additional benefits:

- hyperthermia damages cancer cells
- increases the effectiveness of some chemotherapics (CDDP, MMC, DOX, gemcitabine)
- does not involve increased toxicity
- promotes tissue penetration of chemotherapeutic drugs

In particular, hyperthermia favours drug penetration into the tissues to a depth of 5 mm, a value significantly greater than what occurs in isothermal conditions (2 mm). Therefore the more the peritonectomy is effective achieving “optimal” cytoreduction (CC0 - CC1), i.e. up to allow the total removal of the disease or leaving residues of minimum size (up to 2.5mm), the more associated chemo-hyperthermia will be able to successfully attack microscopic or minimum size tumor residues.

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8. Peritonectomy

The term of peritonectomy identifies precisely the meaning of the surgical procedure: removal of parietal and visceral peritoneum affected by the neoplastic pathology.

Peritonectomy procedures comprise:

- exeresis of parietal peritoneum
- exeresis of visceral peritoneum by visceral and parenchymal resection
- excision/in situ destruction of single implants
- resection of abdominal wall, muscle implants and laparoscopic trocar sites
- lymphadenectomy

At parietal level the procedure entails complete or partial removal of the peritoneum lining the abdominal wall, the diaphragms and the pelvis according to disease extension. General consensus is in removing parietal peritoneum limited to involved areas, sparing a unaffected zones.

If healthy areas are limited, large parietal peritonectomies should be performed up to complete parietal peritonectomy.

In principle, the resection of the parietal and pelvic peritoneum below the transverse umbilical line should be performed in all cases of peritoneal carcinomatosis from ovarian cancer.

Parietal peritonectomy includes greater and lesser omentectomy, resection of round and falciform ligaments, stripping of omental bursa peritoneum.

When PC spreads deeply beyond peritoneal membrane trough abdominal wall, full or partial thickness parietal resection is performed.

Laparoscopic trocar sites are removed by full thickness cylindrical parietal resection when involved by carcinomatosis or when suspected to be contaminated by tumor cells. Umbilicus, regardless its previous use as trocar sites, should be removed on principle in recurrent cases being a frequent site of metastasis.

Visceral peritoneum cannot be separated from underlying visceral tissue and removed separately as with the peritoneum lying the abdominal walls and diaphragms. Therefore visceral peritonectomy involves exeresis of endoperitoneal viscera or organs deeply infiltrated by PC. Rarely and only in special anatomical situations is possible the removal of visceral peritoneum only as when PC does not deeply infiltrate the visceral wall or when it concerned the Glisson's capsule.

Bowel resection is the most frequent peritonectomy procedure in treating peritoneal carcinomatosis from ovarian cancer.

Contemporaneous involvement of multiple viscera induces to multivisceral resections for what en bloc resection should be preferred (Fig 3-4).

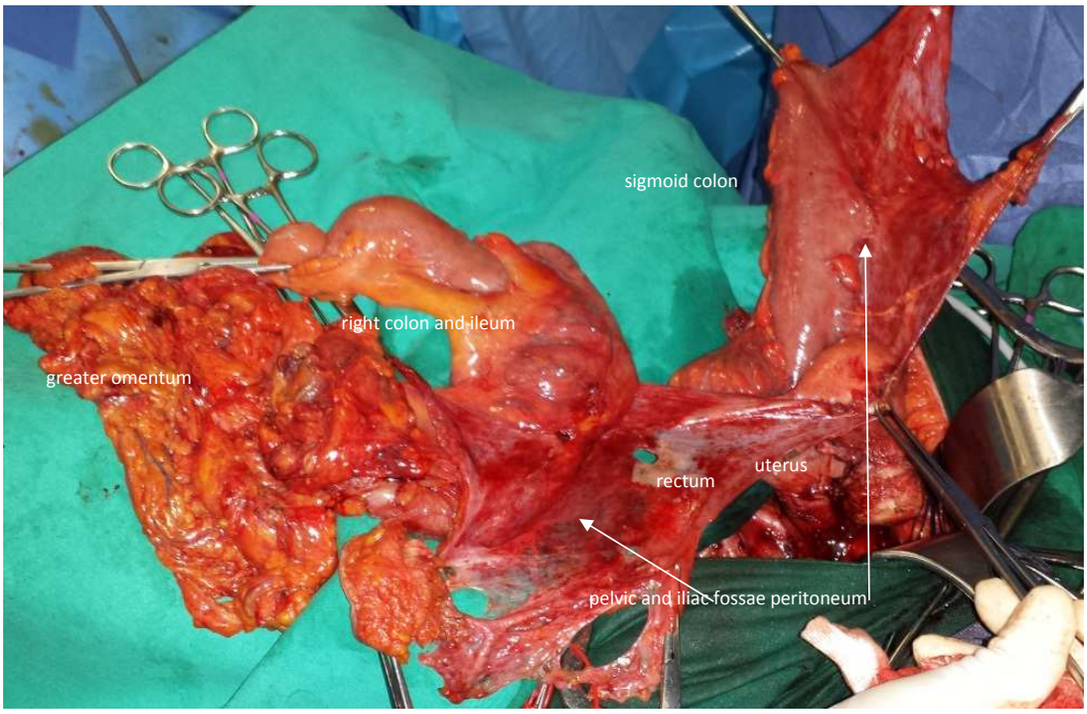

Figure 3. Pelvic peritonectomy: the moment of rectal resection as final step to remove en-bloc the surgical specimen.

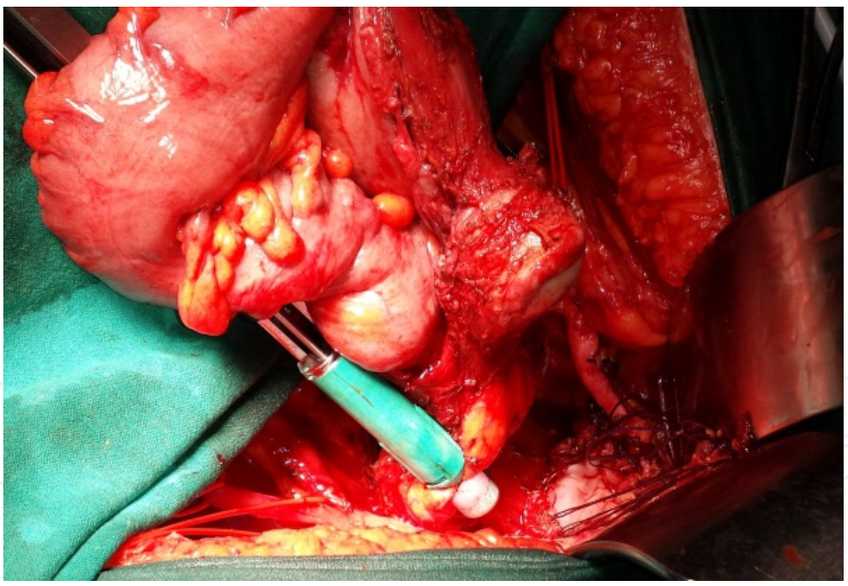

Figure 4. Pelvic peritonectomy: en bloc resection of uterus, adnexa, rectosigmoid colon, pelvic and iliac fossae peritoneum, right colon and greater omentum.

Small and large bowel resections are the most frequent surgical procedures because of deep parietal involvement by tumor implants. Thickness of the gastric wall is such as to allow prevailingly a conservative cleaning of the tumor implants without the need to perform major gastric resections.

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Among large bowel resections, which may include all types of colon resection, left colorectal exeresis is the most frequent. Widespread pelvic involvement by primary tumor and peritoneal metastases with infiltration of the pouch and colorectal wall, provides colorectal resection. Such exeresis should include mesorectal resection and section of mesenteric vessel at their origin to achieve the same radicality requested for primary colorectal cancer treatment. Same radicality criteria should be followed resecting other large bowel sectors. This policy allows to remove both a large amount of mesocolon, frequently infiltrated by implants, and loco-regional lymph nodes which are metastasized in over 50% of cases. [37]

Lymphadenectomy plays a relevant role in strategy of peritonectomy for ovarian carcinomatosis and its prognostic role is highly significant: the only performing the procedure involves a significant increase in survival regardless metastastic involvement of lymph nodes[38-40].

The incidence of loco-regional lymph node metastasis is high exceeding 50% of cases and should induce a policy of radicalization of surgery in lymph nodes as well as in peritoneum.

Iliac-obturator and lumbar lymphadenectomy must be performed routinely in primary forms. In secondary forms lymphadenectomy should be performed if it was not done in previous surgery, or if it has been made necessary by evident nodal relapse in the seats already treated.

Additional forms of lymphadenectomy, at the level of hepatic pedicle, splenic hilum, mesentery or lesser omentum should be performed in the presence of lymphadenopathy macroscopically evident.

9. Removal / “in situ” destruction of implants

The treatment of peritoneal implants does not absolutely require the exeresis of wide portions of peritoneum or the mandatory sacrifice of wide tracts of gut or other structures involved in the disease. In relation to quality, quantity, and macroscopic and microscopic (histology) characteristics of carcinomatous implants, the exeresis should respond to general criteria of saving structures and avoiding useless tissue and visceral sacrifices, when local removal or in situ destruction with an appropriate technology allow a radical result.

A conservative approach is achievable when implants are superficial, few infiltrating the underlying structures, and when are prevailingly mucinous. In these conditions, it is possible to spare wide visceral resection especially when small or large intestine are involved. Local excision or local destruction can be assured effectively with curved scissors, electric scalpels with various tips, radiofrequency (Tissue Link), argon beam laser.

In patients undergone neoadjuvant treatments an additional contribution to HIPEC efficacy is given by argon or electric scalpels use over peritoneal areas where an apparent response to chemotherapy was achieved.

These areas are identified by the presence of specific morphological changes, including opacification, thickening, fibrosis of serous peritoneal membrane and presence of red spots.

Extensive treatment on such areas with argon or ball tip electro-surgery permits diffuse local damage and partial destruction of fibrosis.

The loss of structural continuity will permit a deeper tissue penetration of chemotherapics and a better contact with eventual encapsulated microscopic residuals in post-chemotherapy fibrosis.

10. HIPEC

HIPEC is performed at the end of surgical phase by using a 2.5-4.5 litres solution of chemotherapy drugs. Chemotherapy drugs, HIPEC techniques and duration are synthesized in Table 1. Drug solution is infused in peritoneal cavity by catheters appropriately positioned (fig.5). Infusion is performed under a constant temperature of 41-43°.

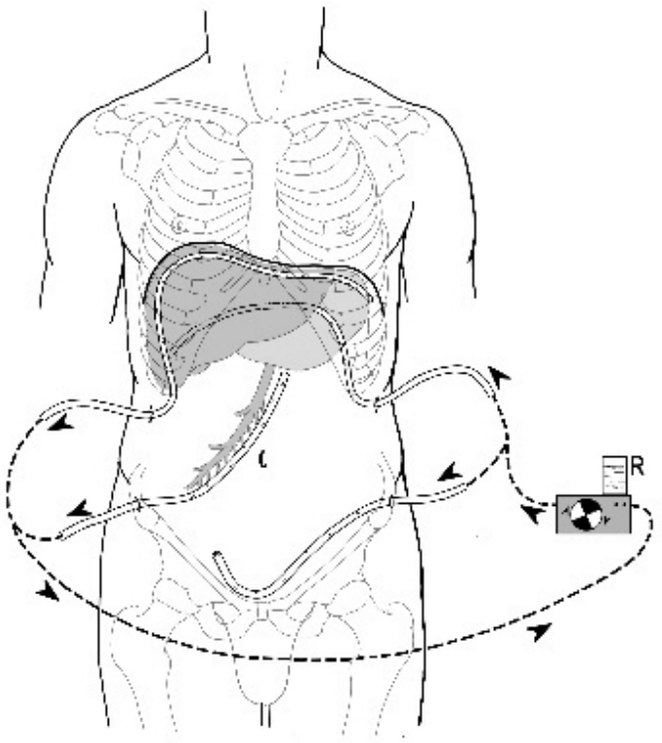

Figure 5. Intra-abdominal catheter position for HIPEC

Open and closed techniques are used for HIPEC but no proven advantage is related to a specific method.

Procedure duration varies from 60 to 90 minutes and CDDP is drug prevailingly administered.

No specific prospective studies have been conducted to verify differences in outcome by specific technique or to test the role of different chemotherapy regimens or drugs.

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STUDY	HYPER-O [44]	DERACO [45]	BAKRIN [42]	DI GIORGIO [48]	DE BREE [43]
HIPEC DRUG					
CDDP	37.2%	-	41%	100%	nr
Oxaliplatin	-	-	21.3%	-	nr
MMC	38.7%	-	2.1%	-	nr
CarboTaxol	14.6%	-	-	-	nr
Doxorubicin	-	-	0.2%	-	nr
Combination (≥2)	9.5%	100%	35.4%	-	nr
HIPEC DURATION					
60 min	-	-	-	100%	nr
60-90 min	45.4%	100%	-	-	nr
90-120 min	54.6%	-	-	-	nr
HIPEC TECHNIQUES					
Open	12.1%	-	68.4%	-	nr
Closed	87.9%	100%	31.6%	100%	nr

Table 1. HIPEC drugs, duration and techniques. nr: not reported.

11. Inclusion and exclusion criteria

General criteria provide to include in the therapeutic program patients without extrabdominal disease with optimal ASA and Performance Status scores and with surgically cytoreducible peritoneal carcinomatosis. Isolated and easy resectable liver metastases are not contraindication to procedure performing when complete cytoreduction can be achieved. High level of PCI is not an absolute contraindication if surgery can obtain optimal cytoreduction although some authors identify levels beyond which the procedure is not advisable[14, 41-42].

Exclusion criteria include:

- great vessels involvement
- massive involvement of small bowel for over 50% of the length or of its mesenteric root
- infiltration of duodenum, pancreas or first jejunal loop
- infiltration of cardia or diaphragmatic pillars
- metastastic lymphadenopathy above the renal vessels
- extra-abdominal metastases

Age and comorbidity are relative exclusion criteria, being ASA and Performance Status scores the most reliable criteria to be considered even in patient in their eighties or suffering of other concomitant diseases.

12. Settings

Peritonectomy combined with HIPEC can be used as primary cytoreduction or as secondary. Primary cytoreduction can be performed as frontline or after neoadjuvant chemotherapy as interval debulking surgery. Secondary cytoreduction is performed in patients with recurrent or persistent disease after previous cytoreductive surgery combined or not with various forms of chemotherapy. Tertiary and quaternary cytoreduction combined or not with HIPEC can be performed in patient with repeated intraperitoneal relapses. PRT + HIPEC can be used as consolidation in primary setting during a second look in patients optimally treated with neoadjuvant chemotherapy or in secondary setting during a second look after any combination of surgery and locoregional or systemic chemotherapy.

13. Results

Over the last 15 years the use of peritonectomy combined with HIPEC has progressively widespread as treatment of peritoneal carcinomatosis from ovarian cancer. Phase III trials about the efficacy of such integrated procedure compared to traditional treatments based on CRS and systemic or normothermic intraperitoneal chemotherapy (IP CHT) are not available. Therefore the role and limits of application of PRT+HIPEC are inferable by results of phase I and mainly phase II studies. At present an overall analysis of the literature allows us to manage data from over 1900 treated cases (Table 2). Collective reviews, multicentric and monocentric case studies are the most available bases to verify the role of PRT combined with HIPEC in treating peritoneal carcinomatosis from ovarian cancer.

Among available collective reviews, the study of de Bree and Helm of 2012 is the more recent and complete. This study is based on 1102 cases collected from 22 monocentric studies and includes the three major previous reviews conducted by Bjelic, Chua and de Bree himself [43, 46-47]. The three multicenter study published between 2010 and 2013 are reported; their study designs were retrospective or prospective phase II. As for monocentric studies, results of a clinical phase II prospective study about the use of PRT and HIPEC in treating peritoneal ovarian carcinomatosis performed by the authors of this chapter is reported. This study is based on 130 cases treated between November 2000 and December 2013 in the same center and by the same staff [48]. This is the largest monocentric case study compared to all other reports included in the collective review of de Bree, the major of which consists of 81 cases.[49]

The multicenter study of Deraco includes exclusively cases undergoing primary CRS as front line, while that of Bakrin comprises prevailingly cases treated for recurrence (83,8%). In the other studies the rates of primary and secondary CRS were almost similar.

http://dx.doi.org/10.5772/60844

Author Year	**De Bree 2012 [43]**	**Helm (HYPER-O) 2010 [44]**	**Deraco 2011 [45]**	**Bakrin 2013 [42]**	**Di Giorgio 2014 [48]**
Type of study	Collective Reviews	Multicenter	Multicenter	Multicenter	Monocentric
Study Design	Collection of phase II studies	Retrospective	Prospective phase II	Retrospective	Prospective phase II
Frontline	18.4%	18.5%	100%	2.1%	17.7%
Interval debulking	5.6%	13.6%	-	4.2%	29.2%
Consolidation	8.9%	8,6%	-	9.9%	5.4%
Recurrence	67.1%	5.3%	-	83.8%	47.7%
No. Cases	1102	141	26	566	130

Table 2. PRT + HIPEC for peritoneal carcinomatosis from EOC: literature review.

PCI mean ranged from 10.6 to 16.3 and in all series the rate of patients classified as FIGO stage III and IV exceeded 90 %(Tab.3).

Author Year	**De Bree 2012 [43]**	**Helm (HYPER-O) 2010 [44]**	**Deraco 2011 [45]**	**Bakrin 2013 [42]**	**Di Giorgio 2014 [48]**
No. Cases	1102	141	26	566	130
PCI mean	nr	nr	15.5(5-26)	10.6(0-31)	16.3(0-39)
CC score 0 =1 >1	nr	58.3% 15.1% 26.6%	57.7% 42.3%	74.9% 17.9% 7.2%	66.7% 20% 13.3%
Platinum response *resistant* *sensitive* *undetermined*	nr	34% 53.9% 12.1%	nr	52.1% 47% 0.9%	36.8% 53.8% 9.4%
Adjuvant Chemotherapy yes no	nr	93.6% 6.4%	100%	28.3% 71.7%	71.5% 28.5%

Table 3. Patients characteristics. nr: not reported.

Peritonectomy was able to achieve optimal cytoreduction in most cases and the rates of complete cytoreduction ranged from 57,7 to 74,9, being the better scores related to lower level of PCI mean.

Platinum based drugs were the most used during HIPEC, alone or in combination with other chemotherapics. Adjuvant systemic chemotherapy was administered in post HIPEC phase in the vast majority of cases.

14. Survival

Results related to survival are synthesized in Tab 4 - 6.

Author - Year	Helm (HYPER-O) 2010 [44]				Bakrin 2013 [42]	
Survival	5 yr OS %	Median OS months	5 yr PFS %	Median PFS months	5 yr OS %	Median OS months
Frontline	33.3	41.7	19.7	24.8	33.7	52.7
Interval debulking	50.2 25.4	68.6 30.3	9.6 13	16.8 13.7	16 17	36.5 35.4
Consolidation	42.4	53.7	24.2	29.6	12.5	33.4
Recurrence	18	23.5	9.6	13.7	37	45.7
CC0 Primary	26.7	37	-	-	23.6	41.5
CC0 Recurrence			-	-	40.2	51.5
Author – year	Deraco 2011 [45]					
Survival	5 yr OS %	Median OS months	5 yr PFS %	Median PFS months		
Frontline	60.7	not reached	15.2	30		

Table 4. PRT + HIPEC for peritoneal carcinomatosis from EOC: survival in multicentre studies.

Author - Year	De Bree 2012 [43]			
Survival	5 yr OS %	Median OS Months	5 yr PFS %	Median PFS months
Frontline	47	33	17,5	25
Interval debulking	54 58.5	69 66.5	10 36.5	17 35
Consolidation	84	64	63	35
Recurrence	33	42.5	11.5	20.5
CC 0 Primary	-	66 (only frontline)	-	-
CC 0 Recurrence	-	-	-	-

Table 5. PRT + HIPEC for peritoneal carcinomatosis from EOC: survival in collective reviews

http://dx.doi.org/10.5772/60844

Author – year	Di Giorgio 2014 [48]							
Survival	5 yr OS %		Median OS Months		5 yr PFS %		Median PFS Months	
Frontline	57.6		63.1		38		38.5	
Interval debulking	41.2	50.7	37.4	61.1	39.7	43.1	21	38.5
Consolidation	-				-			
Recurrence	45		40		29.5		17.7	
CC0 (primary)	59.6		50.5		53.7		56.8	
CC0 (recurrence)	61.3		66		42.2		52	

Table 6. PRT + HIPEC for peritoneal carcinomatosis from EOC: survival in author's monocentric study.

In all studies except one, patients treated in primary setting tend to survive more than recurrent; only Bakrin reported better 5- year overall survival in secondary setting (Fig 6).

In an half of reports, 5- year overall survival rate was about 50 % after primary CRS and about 40% after secondary CRS. Overall PF survival ranged across the reported studies between 13 to 43.1% at 5 years.

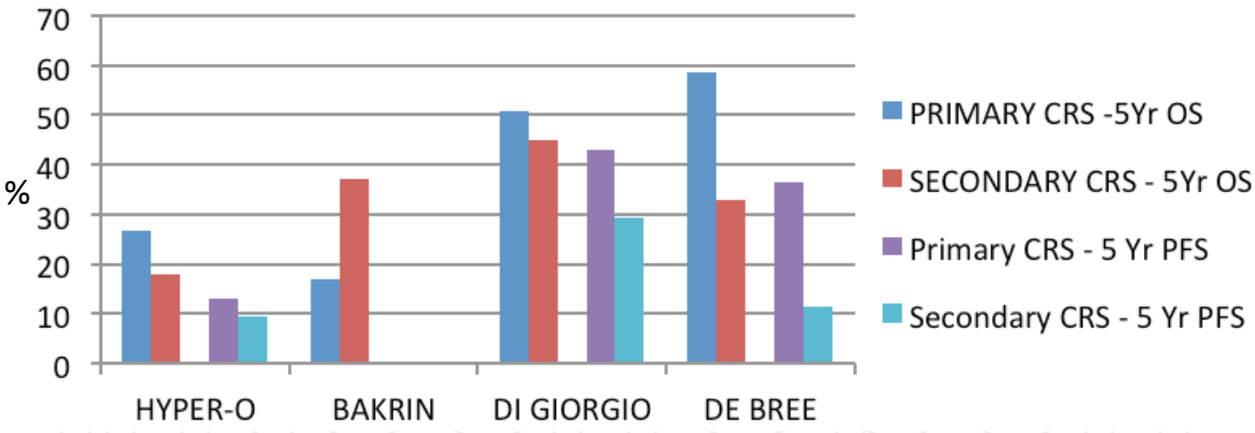

Figure 6. yr Overall and Progression Free survival after primary and secondary CRS +HIPEC

The values of median survival, both overall and progression free, reflected the general trend of 5-year survival: except for Bakrin's study, patients treated in primary setting survived more than patients treated for recurrence (Fig. 7).

Among patients treated in primary setting, patients undergoing PRT and HIPEC as front line tended to survive more than those neoadjuvated. Data from HYPER-O report are not available by admission of their Authors because of the small number of events

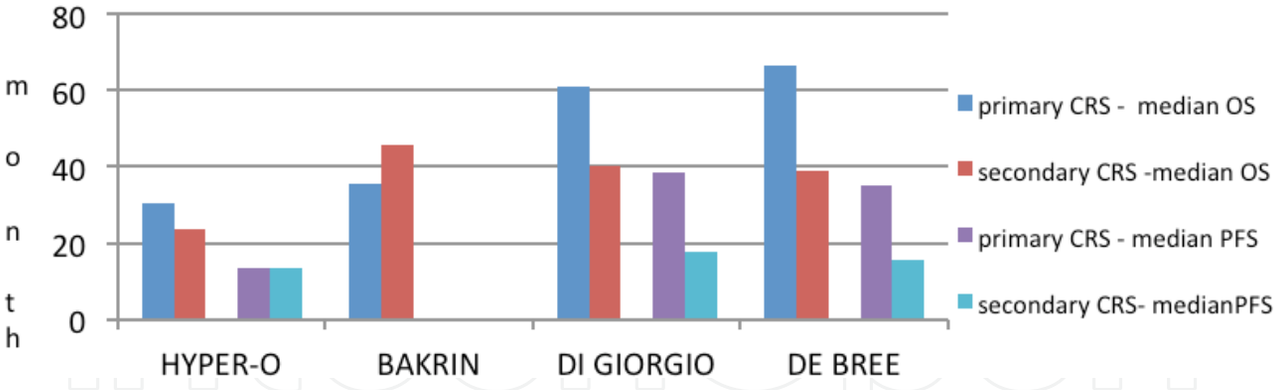

Figure 7. Median Overall and Progression Free survival after primary and secondary CRS+HIPEC

Results about long term prognosis in patients with PRT and HIPEC administered as consolidation during a second look are not useful for an advisable evaluation because of scarce number of treated cases in all analyzed studies.

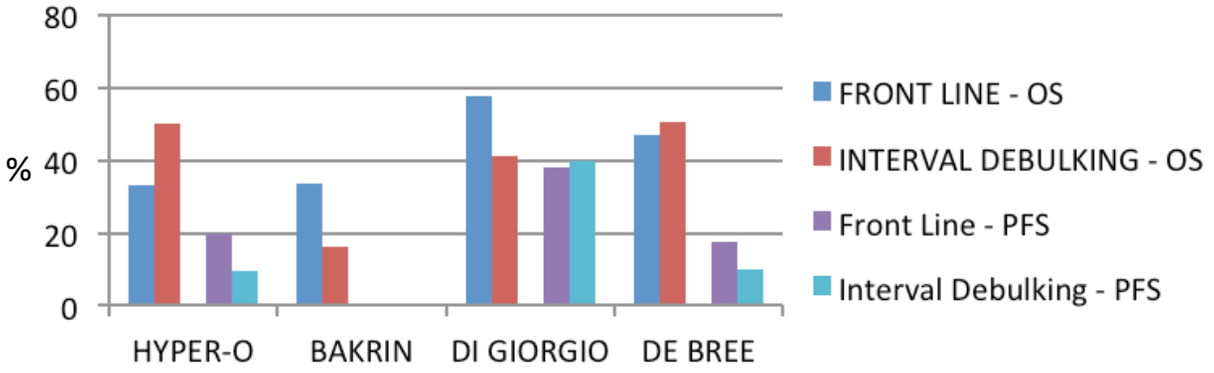

Figure 8. yr Overall and Progression Free survival in primary setting

14.1. Prognostic factors

A lot of potential prognostic factors have been analyzed by uni- and multivariate analyses and completeness of surgical cytoreduction (CC) resulted as the most significant prognostic factor in all series. Among the others, PCI was significantly related to survival in 3 of the 4 studies where has been analyzed.

Platinum response, blood loss, level of bowel wall infiltration by tumor implants, lymph node metastases, use of carboplatin and duration of perfusion, correlated significantly with survival at least once across the study by uni- or multivariate analyses.

14.2. The role of completeness of cytoreduction and PCI

Since 1970s results of treatment of locally advanced epithelial ovarian cancer emphasized the role of surgical debulking aimed not only at palliation of clinical status borned from intraper-

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Author Year	De Bree and Helm 2012 [43]	Helm (HYPER-O) 2010 [44]	Deraco 2011 [45]	Bakrin 2013 [42]		Di Giorgio 2014 [48]	
Prognostic Factors				Primary	Recurrence	Primary	Recurrence
CC score	nr	0.025	nr	0.005	0.0001	0.003	0.009
PCI	nr	nr	nr	0.0012	0.0001	0.008	0.007
PS	nr	nr	nr	ns	0.0224	ns	0.006
Setting	nr	ns	nr	nr	nr	ns	ns
Platinum response	nr	0.048	nr	nr	ns	0.0005	ns
Blood loss	nr	0.005	nr	nr	nr	ns	0.0004
Ca125	nr	nr	nr	0.0241	0.2131	ns	ns
Lymph node metastases	nr	nr	nr	nr	nr	0.002	ns
Age	nr	nr	nr	0.0574	0.0314	ns	ns
Bowel wall infiltration	nr	nr	nr	nr	nr	0.0002	0.01
HIPEC drugs number	nr	nr	nr	0.9689	0.0176	ns	ns
HIPEC drug type	nr	0.011	nr	0.2653	0.7098	ns	Ns
Duration of perfusion	nr	0.047	nr	nr	nr	ns	ns

Table 7. PRT + HIPEC for peritoneal carcinomatosis from EOC: prognostic factors by uni or multivariate analyses. [nr: not reported; ns: not significant]

itoneal disease spread but also to improve long term survival. [50]. The concept of optimal cytoreduction correlated to the dimension of tumor residuals among gynecologic oncologist has progressively induced to reduce from 2 cm to 0.5 cm the maximum acceptable limit. Among surgical oncologist according to Sugarbaker classification such limit is up to 2.5 mm. The role of cytoreduction level in primary resection for locally advanced EOC is well highlighted by the most relevant retrospective and prospective studies reported in literature [51-53].

A meta-analysis of 6.855 cases confirmed these data [54]. The most significant gap was observed between patient without any residue and those with residues of any size. Even in patients undergoing cytoreductive surgery for recurrent disease a lot of retrospective studies [21-30] and a meta-analysis including 2.019 patients [55] confirmed the prognostic role of maximal cytoreduction. Maximal or optimal cytoreductive surgery are correlated to evident advantages improving patients quality of live, decreasing drug resistance clones entity and improving chemotherapy efficacy. Complete removal of peritoneal disease proves to be the

most relevant prognostic factor in all setting even in all analyzed studies on HIPEC here reported (Tab 6).

Some authors argued about the role of PCI in selecting patients to be treated with peritonectomy and HIPEC, identifying level of diffusion of peritoneal disease by scores beyond which such combined procedures should be avoided. In particular Bakrin identified in a value of PCI equal to 10 that limit in relation to related poor prognosis, while other authors [14] identify specific laparoscopic scoring of diffusion of peritoneal carcinomatosis to predict the achievement of an optimal cytoreduction.

Results of our monocentric study show that in PC from ovarian cancer high degrees of PCI are not an absolute limit to the execution of the procedure, if it is possible to obtain an optimal cytoreduction. We believe that high degree of PCI does not constitute an absolute contraindication to cytoreduction, as some claim [41, 56] and that rather one should take greater account of technical feasibility, quality of carcinomatosis of the individual case and possibility of obtaining an optimal cytoreduction. In our series, which had a PCI mean of 16.3, patients with PCI> 16 have nevertheless demonstrated a 5-year overall survival of 24.3%, with no difference between primary and secondary CRS, and a 5 year survival of 50.2 % (median 61.1 months) when in these patients with high PCI a complete cytoreduction (CC0) was obtained.

14.3. The role of NACT

Diffuse Peritoneal Carcinomatosis in primary setting is ideal target for neoadjuvant chemotherapy with carboplatin and taxol, due to high rate or responsiveness when administered as first line treatment (> 80%).

Nevertheless advantages of such strategy are not clear and results are conflicting, both in patients treated with and without HIPEC.

In patients undergoing NACT and successively treated with standard cytoreductive surgery and systemic chemotherapy, preoperative chemotherapy failed to improve survival. In EORTC 55971 phase III trial, NACT increased the rate of optimal Cytoreduction and decreased post-operative morbidity compared to front line CRS, but did not influence Overall or PF survival [57-58].

Similar results have been observed also in the studies related to the role of NACT in patients treated with PRT + HIPEC[59-60].

A better comprehension of significance of this strategy may drawn from analysis of chemosensitivity during NACT. In our monocentric series more than 50% of patients treated in primary setting undergo carbo-taxol-based NACT. 26,3 % didn't respond to this regimen and demonstrated a significant worse prognosis (29,4% 5-yr OS) compared to cases treated front line or NACT responders (56,4% 5-yr OS).

Some studies envisage for NACT disadvantages related to increased risk of platinum resistance during post-CRS adjuvant chemotherapy [61] or post-NACT histological changes occurring in tumor tissue that correlate with a poor prognosis [62]. These data are reflected in our cases: neoadjuvated patients showed a higher percentage of chemoresistance during post-HIPEC treatment with platinum derivatives (41.7%) than those not neoadjuvated (31.8%) and survived less.

http://dx.doi.org/10.5772/60844

In the near future the results of ongoing trials will better highlight the optimal strategy in using NACT. Based on results of studies now available, NACT regimen should be personalized and administered to patients with bulky intraperitoneal disease at risk of incomplete CRS, or to patients with small metastatic pleural effusion or with small isolated liver metastasis easily resectable during CRS.

14.4. The role of platinum chemoresistance

The role of platinum chemoresistance has been analyzed in three studies and in two of them chemoresistance resulted as a negative prognostic factor [44, 48 - Tab 6]

In two studies platinum chemoresistance was analyzed in pre-HIPEC phase in patients treated for recurrence while in our monocentric study we have evaluated the chemoresistance by referring to the recurrence/progression within six months after the end of post-HIPEC adjuvant treatment with platinum-based drugs, both in primary and in recurrent forms.

In the two multicenter studies where chemoresistance was analyzed in pre- HIPEC phase, it didn't influence survival in Bakrin's report while resulted marginally significant in HYPER-O registry.

In our series,Platinum chemoresistance so assessed was related to a worse prognosis only after primary CRS plus HIPEC, with both univariate and multivariate analyses (Table 6). The negative correlation between platinum chemoresistance and prognosis in primary forms can be partly explained by the possibility that NACT determines chemoresistance against the platinum used in systemic form after CRS as described above [62].

In our series, post-HIPEC chemoresistance did not influence significantly survival of recurrent patients, whose rates of platinum chemoresistance and chemosensitivity were similar (47.2% vs 52.8%).

In patients treated for recurrence, PRT combined with HIPEC may induce, especially for cases CC0, a reset of previous oncologic situation and that the chemosensitivity assessment to platinum based drugs chemotherapy post-HIPEC more faithfully represents the new relationship between patient and such chemotherapics. Moreover, the possibility that the CRS associated with HIPEC may lead to a retrieval of chemoresistance to platinum is theorized by some authors [54].

14.5. The role of bowel wall infiltration

Among the analyzed studies carcinomatous infiltration of intestinal wall has been analyzed only in our monocentric study. Progressive infiltration of bowel wall influenced negatively long term survival. The impact of the degree of parietal layers infiltration like the T role in TNM staging of gastro-intestinal tumor but in an inverse sense has been analyzed in previous report by us and other authors in relation to only colorectal resection [63-65]

Recently the evaluation of bowel wall infiltration up to the mucosa has been included in new 2014 FIGO stage for ovarian cancer identifying mucosal infiltration as FIGO stage IVb [1,2].

14.6. The role of lymphadenectomy

The role of lymphadenectomy and significance of lymph node metastatic involved in locally advanced EOC is controversial. Lymphadenectomy is supported from some authors on the basis of its positive influence on survival [66-67], while other authors are skeptical [68]. The high rate of loco-regional lymph node metastases justify systematic lymphadenectomy in primary setting on principle and in secondary setting when not performed during primary cytoreduction.

The significance of lymph node metastasis was analyzed only in our monocentric study, where iliac-obturatory and lumbar lymphadenectomy was performed routinely in primary settings and when not done in previous CRS in patients treated for recurrence. Colorectal resections were routinely performed with radical technique as previously reported. Lymphadenectomy in other districts such as the hepatic pedicle, perigastric or mesenteric stations were performed when necessary.

In our study, overall 52,6% of patients had lymph node metastases without significant differences between primary or recurrent forms, similarly to what reported in the literature [45]. Although lymph node involvement worsened prognosis, related 5-year Overall survival reached 39,6% corroborating the role of lymphadenectomy.

15. The role of HIPEC — Comparison of HIPEC vs no HIPEC

Overall, the results so far obtained by using of PRT combined with HIPEC in treating peritoneal carcinomatosis from ovarian cancer even available mainly if not exclusively from non randomized prospective studies show progressive improvement of long term survival both in primary or recurrent forms in high volume activity centers [55].

Although general consensus about the role of maximum cytoreduction is at present undisputable, criticism about HIPEC role is diffuse because of its potential high morbidity risk and lack of prospective controlled studies.

At present both in primary and recurrent settings, a series of cases / controls studies has demonstrated the major efficacy of the association between CRS and HIPEC compared to traditional treatments [69-76]. Results of the first phase III prospective study recently published [77] about this topic confirmed a significant improvement in long term survival in patients treated with HIPEC compared with those undergoing traditional treatment with CRS and adjuvant systemic chemotherapy.

16. Morbidity and mortality

Peritonectomy and HIPEC are integrated in a complex and aggressive procedure whose specific related complications are difficult to distinguish, being the overall morbidity reason-

http://dx.doi.org/10.5772/60844

ably related to the whole procedure. Therefore if renal and haematological toxicity have to be related specifically to chemotherapy activity, even for most common surgical complications like anastomotic leak, intestinal fistulas or endoperitoneal haemorrhage, HIPEC influence can't be undervalued.

Overall the incidence of major complications (grade 3 and 4) ranged from 14% to 56% whose treatment provided surgical, radiological or endoscopic re-intervention in a percentage ranging from 13% to 19,2%.

Haematological and renal toxicity accounted for a maximum incidence of 11 and 8 % respectively.

Mortality rate was extremely variable ranging from 0 to 10%.

It is difficult to compare various experiences mainly because of different criteria by which complications are defined and of different classifications with which morbidity levels are synthetized. The number of possible complications after PRT + HIPEC is high and the likely to have a complete scenarios of all adverse events is difficult and depends on the accuracy with which databases are prepared and on the prospective or retrospective modalities with which data are updated.

A detailed example of database dedicated to morbidity is described in the book edited in 2013 by Sugarbaker about the treatment of peritoneal carcinomatosis [78] with an indication of 48 adverse events arranged within 9 categories. Each adverse event is graded with a score from I to IV, and 14 prognostic indicators have been used in uni and multivariate analyses with the aim to identify the most significant risk factors for postoperative morbidity and mortality.

It is an interesting try to organize the adverse events but results difficult to reproduce and not yet used in other studies. Its use can be considered particularly important for studies dedicated to this problem. An acceptable compromise to obtain comparable data can be gained by using of more simplified and diffused classifications of complications, such as that of Dindo's or CTCAE, and by performing multivariate analyses to infer the risk factors for various complications.

Among the analyzed studies, only Bakrin's multicentre study and the author's monocentric study reported the results of uni or multivariate analyses on risk factors and PCI and CC score resulted as the most significant parameters correlated to an increased occurrence of major complications. Cascales Campos on 91 patients treated with PRT + HIPEC for ovarian carcinomatosis in various settings [76] has confirmed with multivariate analysis the role of PCI as risk factor for major complications, associated to the performing of digestive anastomoses.

These results reliably correlate with operative mortality and re-intervention rates, as reported in Deraco and Di Giorgio's studies that include cases with highest mean of PCI, and with lowest morbidity rate in patients treated as consolidation which are free of disease at second look. An exception is represented by Pomel's prospective study dedicated to cases treated as consolidation with Oxaliplatin based-HIPEC (CHIPOVAC); the study was stopped for excessive morbidity. (70)

The duration of procedure resulted as risk factor in the monocentric study, as in other reports about using of PRT + HIPEC in both ovarian and extra-ovarian PC [72-74].

Among major complications, the anastomotic dehiscences are the most dangerous for concomitant risk of severe sepsis and postoperative mortality. Risk factors for these events are numerous and correlate with the extension of carcinomatosis, the number of intestinal resections required for cytoreduction, the duration of procedure, the blood loss, the extensive use of in situ destruction of parietal implants, the type of anastomosis, in particular, colorectal, the lack of adequate bowel cleaning in occluded and sub-occluded patients, the previous treatment with bevacizumab.

The containment of the risks lies in reducing the number of anastomoses with appropriate evaluation of the intestinal tracts to be resected and avoiding the simultaneous performing of multiple digestive anastomoses in conjunction with low colorectal anastomosis. In these cases it is strategically correct to perform a colorectal resection according to Hartmann and delay recanalization in a second intervention after the end of adjuvant treatment and after further 6 months follow up [65].

In summary, also in presence of remarkable variability of data from the analyzed studies, the incidences of complication and mortality appear limited and comparable to those related to major abdominal and pelvic surgery. Morbidity rate control is possible in highly active centers with consolidated experience and specialized medical, nursing and logistic organization. Results of trials in progress on the specific role of HIPEC shall furnish also significant data about HIPEC related morbidity, while the use of specific protocols and prospective databases, connected to multi-institutional experiences, can give useful data to limit morbidity in medium period.

17. Future

The use of PRT combined with HIPEC for treating peritoneal carcinomatosis from ovarian cancer is being widely diffused thanks to promising results in terms of survival but is not without its critics that are primarily focused on the role of HIPEC. To date, the major criticisms about HIPEC involve its potential influence on survival and morbidity and the lack of prospective randomized studies as support of results of this procedure. The differing opinions between oncological surgeons, who are more likely to use HIPEC, and oncologic gynecologists and medical oncologists, who are more likely to use standard treatment with CRS and systemic CHT or, more rarely, isothermic IP-CHT, plays a relevant role in such a scenario. Therefore, it is necessary to verify whether PRT plus HIPEC can guarantee better survival compared with standard treatments and whether the incidence of related morbidity is acceptable in comparison with other types of treatment. At present many clinical trials are ongoing about the efficacy of PRT and HIPEC, most of them are focused specifically on HIPEC role, both in primary and in recurrent patients (Tab 8).

http://dx.doi.org/10.5772/60844

Studies	Time	Drug	Type of study	Identification number*
Safety and Pharmacokinetics of Intraoperative Hyperthermic Intraperitoneal Chemoperfusion (HIPEC) With Cisplatin to Treat Platinum-sensitive Recurrent Ovarian Cancer	Recurrence	Cisplatin	Non-Randomized	NCT01387399
Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence (HORSE)	Recurrence	Cisplatin	Randomized	NCT01539785
Intraoperative Hyperthermic Intraperitoneal Chemotherapy With Ovarian Cancer	Primary Recurrence	Cisplatin	Randomized	NCT01091636
Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer (Chorine)	Primary	CDDP+ Paclitaxel	Randomized	NCT01628380
Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer	Recurrence	-	Randomized	NCT00426257
Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)	Recurrence	Cisplatin	Randomized	NCT01376752
Feasibility Study of HIPEC for Patients With Stage III or Only Pleural Stage IV Ovarian Carcinoma in First Line Therapy	Primary	Cisplatin	Safety/Efficacy	NCT01709487
WCC# 59 Hyperthermic Intraperitoneal Chemotherapy Utilizing Carboplatin in First Recurrence Ovarian Cancer	Recurrence	Carboplatin	Safety/Efficacy	NCT01144442
Outcomes After Secondary Cytoreductive Surgery With or Without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Followed by Systemic Combination Chemotherapy for Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Recurrence	Carboplatin	Randomized	NCT01767675
A Phase II Combined Modality Protocol of Debulking Surgery With HIPEC Followed by Intraperitoneal Chemotherapy for the Treatment of Recurrent Ovarian, Primary Peritoneal & Fallopian Tube Cancers	Recurrence	Cisplatin	Safety/Efficacy	NCT01659554

Studies	Time	Drug	Type of study	Identification number*
Quality of Life and Survivorship Care in Patients Undergoing Hyperthermic Intraperitoneal Chemotherapy (HIPEC)	Primary Recurrence	-	Efficacy	NCT01126346
Surgery and Chemotherapy With or Without Chemotherapy After Surgery in Treating Patients With Ovarian, Fallopian Tube, Uterine, or Peritoneal Cancer	Primary Recurrence	Cisplatin	Safety	NCT01970722

Table 8. Ongoing clinical trials on HIPEC in EOC. [79-90]

Results of such trials may help to confirm the role of HIPEC in various subsets of patients treated in primary setting and contribute to specify also the prognostic role of NACT and chemoresistance.

An half of ongoing studies are referred to recurrent patients. In the most of such trials, only platinum sensitive recurrences are considered. All of these studies are aimed to evaluate the prognostic role of HIPEC in terms of OS, PFS and DFS, having a variety of secondary outcomes such as the role of different combinations of chemotherapy drugs, the use of IP CHT after HIPEC, the QoL, toxicity and morbidity.

18. Conclusions

At present, lacking results of prospective randomized phase III studies, the role of PRT and HIPEC in treating peritoneal carcinomatosis from EOC can be reliably evaluated by the studies reported in this research which include over 1900 treated cases. The overall size of these case studies is a solid base to reliably identify the trend of results regardless of the study limitations discussed above.

On the basis of analysed results, following conclusions can be drawn:

- PRT plus HIPEC guarantee significant percentage of long-term overall and progression free survival in primary and recurrent settings.
- In all settings, complete cytoreduction represents the most significant prognostic factor.
- High PCI levels do not constitute a limitation for this procedure if optimal CRS is technically feasible.
- The prognostic role of NACT and Platinum-based chemoresistance is uncertain; but NACT and platinum chemoresistance should be better assessed, the first for when to be applied and the other for its application even in post-HIPEC setting

- Major complications and mortality rates are similar to those related to major abdominal pelvic surgery and are not different after primary or secondary cytoreduction. PCI and CC scores represent the most significant risk factors for major complications.

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